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High π-Route Reactivity In The Tropene System. Absence Of A Nitrogen Acceleration Effect.[1]

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Respectfully dedicated to Professor Gabor Fodor on the occasion of his 75th birthday.

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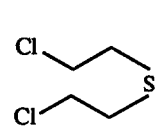
Abstract: *Solvolyses of a suitably constructed tropene tosylate and its unsaturated carbocyclic analog show that the amino function, despite its suitable spatial location, does not enhance the π-route assistance but reduces it slightly.*

Thio and amino substituents located β to a leaving group as in **1** dramatically accelerate the hydrolyses of these substances.[2,3] A more distant heteroatom[3b] can also confer substantial rate enhancement. Similarly, a remote double bond can accelerate the departure of a leaving group, as found with the homoallylic anti-7-norbornenyl tosylate **2**,[4] or the 2-(Δ^3-cyclopentenyl)-ethyl system **3**.[5] In the present paper we address the possibility that a suitably poised amino group could enhance the nucleophilic π-interaction between a double bond and a developing cationic center. To this end we prepared the unsaturated tropane alkaloid[6] derivative **4** and its saturated counterpart **5** and examined their solvolyses. As a reference compound we also synthesized and studied



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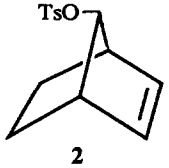

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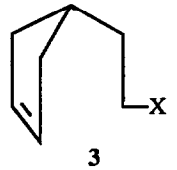

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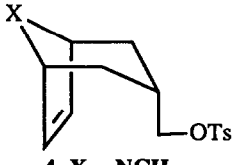
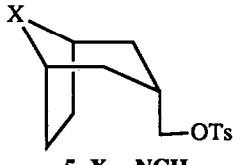
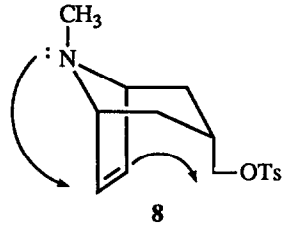


4 X = NCH_3
6 X = CH_2



5 X = NCH_3
7 X = CH_2



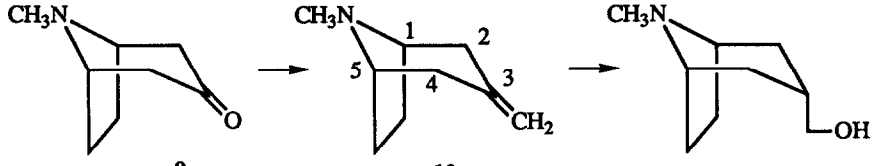
8

the corresponding unsaturated carbocyclic system **6**. The issue is whether or not the unshared electrons on nitrogen can interact synergistically with the olefinic π-cloud to enhance the nucleophilicity of the double bond (as suggested by **8**). Our findings reveal that although the double bond in **4** (and in **6**) accelerates ionization dramatically relative to their saturated counterparts **5** and **7**, the substitution of the CH_2 group in **6** by the CH_3N in **4** actually *reduces* reactivity by *ca.* eight-fold. The saturated carbocyclic derivative **7** was not examined in our laboratory, but its rate of solvolysis was estimated from that of the corresponding brosylate, which had been investigated by Sargent and Johnson.[7]

Results and Discussion

The Saturated Nitrogen Analog 3α-Hydroxymethyltropane Tosylate (5). 3-α-Hydroxymethyltropane (**11**) was obtained in 86% yield by hydroboration of 3-methylenetropane (**10**) with disiamylborane[8] followed by oxidation (Scheme 1). Thus, N-oxide formation did not compete effectively. Our material gave mp 75-76° as reported by Zirkle *et al.*[9] Alkene **10** was prepared by the Wittig reaction of tropane-3-one (9). The use of n-butyllithium to generate the ylide gave **10** in 50% yield, which was increased to 86% when the ylide was generated with tBuOK as suggested by Schlosser and Christman.[10] Treatment of alcohol **11** with brosyl chloride in pyridine or in triethylamine gave brosylate in a maximum yield of 45%. The reason for the low yield is not clear. A superior approach was to prepare the lithium salt of **11** with *n*-butyllithium and then add the arylsulfonyl

Scheme 1

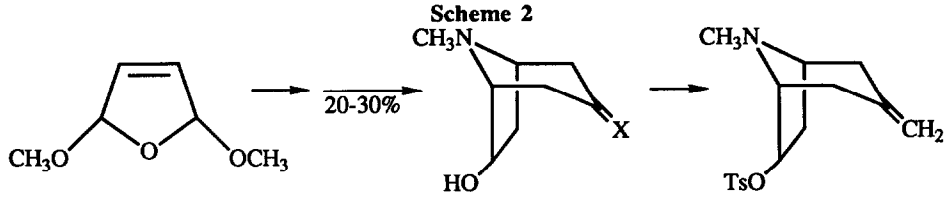


9 **10** **11**

chloride. We used this procedure to prepare the tosylate **5** (76% yield) instead of the brosylate, because we subsequently found that the *unsaturated* brosylates were too reactive. A stable hydrochloride salt of **5** was also obtained.

The Unsaturated Nitrogen Model Compound 3α-Hydroxymethyltrop-6-ene Tosylate (4). Several plausible, short synthetic routes proved unsatisfactory. The successful route (Scheme 2) involved tropan-6β-ol-3-one (**13**), which we obtained in 20-30% yield by the Robinson-Schopf condensation of hydroxysuccinic dialdehyde (from **12**) with methylamine and acetonedicarboxylic acid as described by Nedenskov and Clauson-

Scheme 2

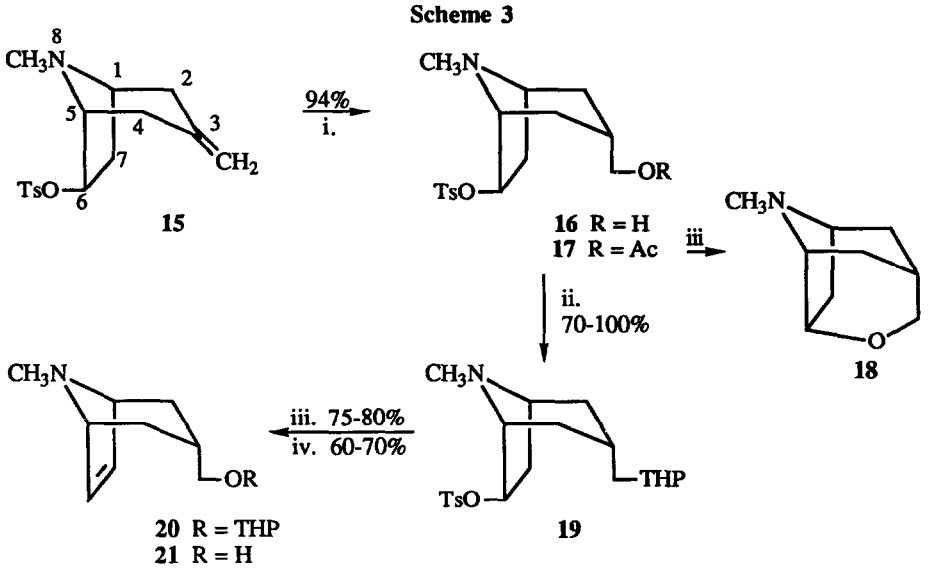


12 **13** X = O, **14** X = CH_2 **15**

Kaas.[11] This reaction has been used by others to make tropan-3-one functionalized at C-1 or C-6, or difunctionalized at C-6 and C-7.[12] Other procedures gave tropane skeletons, but they had not been used to prepare 6-substituted tropanes.[13,14] Wittig reaction of **13** by the t-BuOK method gave olefin **14** directly in 82% yield. Interestingly, only a slight molar excess of ylide was required, because it did not react with the hydroxyl of **13**. The tosylate **15** was prepared in 50% yield with Py/TsCl, but in 88% yield with n-butyllithium/TsCl. Elimination with t-BuOK/DMSO converted **15** rapidly to a diene. Hydroboration of **15** with excess disiamylborane and oxidation gave **16** (94%) (Scheme 3). The product would not crystallize and an elemental analysis was not attempted. We accept that the hydroxymethyl group is in the α-configuration in **16** by analogy to our hydroboration of **10** to **11** (Scheme 1), and from evidence presented later. Alcohol **16** was converted to a liquid

acetate **17**. We next heated this tosylate-acetate in collidine containing dimethylaniline (190°, 2.5 h) to form the 6,7-double bond. (This procedure was used by Fodor, *et al.*[15] to convert 6β-bromotropan-3α-ol acetate to trop-6-ene-3α-ol acetate.) This approach was unsuccessful as was also the treatment of **17** with t-BuOK/DMSO, which

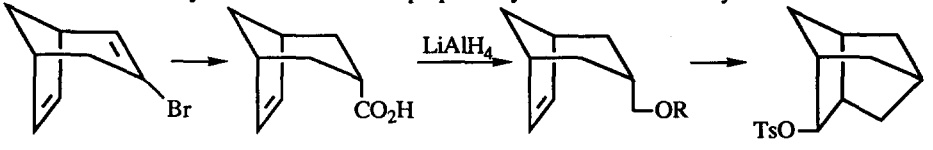
Scheme 3



i. Hydroboration-Oxidation **ii. Dihydropyran/tosic acid**
iii. tBuOK/DMSO **iv. H_3O^+, MeOH-H_2O**

gave a tricyclic ether **18**. The tricyclic ether obtained serendipitously gave further support for the α-configuration at C-3 in **16**. Alkene **20** was generated by conversion of **16** (Scheme 3) to the tetrahydropyranyl ether **19**,[16] followed by smooth elimination with tBu/OK/DMSO. The THP protecting group was removed by methanolysis in acid. Excess acid was avoided to suppress possible formation of the tricyclic ether. The alcohol **21** gave a singlet at δ 5.89 for the olefinic hydrogens. Hydrogenation of **21** gave authentic 3α-hydroxymethyltropane **11**.[17] We were unable to prepare the brosylate of alcohol **21** probably because of its high reactivity. However, the tosylate **5** was obtained in high yield, was characterized by ir and nmr, and was converted to a crystalline hydrochloride for storage. The spectra and elemental analysis of this salt showed no evidence of decomposition or rearrangement during its preparation and purification.

The Unsaturated Carbocyclic Analog 3α-Hydroxymethylbicyclo-[3.2.1]oct-6-ene Tosylate (6). Unsaturated carbocyclic alcohol **24a** was prepared by lithium aluminum hydride reduction of the 3α-unsaturated



22 **23** **24** **25**

a, R = H; b, R = Ac
c, R = 3,5-DNB

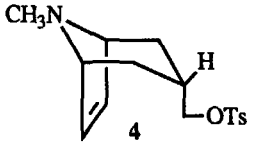
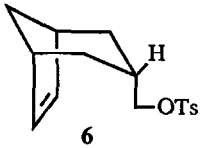
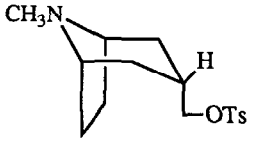
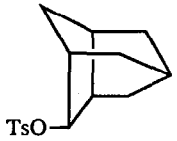
acid **23**[18,19] which they prepared from **22**.[20] We introduced two improvements: (1) the enolate dianion precursor of **23** was quenched with t-butyl alcohol affording a higher ratio of **23** to its β-epimer; and (2) the pure iodolactone was converted to **23** with Zn/HOAc[21] instead of Zn/EtOH.[19] Our yield of **23** was double the reported value.[19] The ^{1}H nmr of alcohol **24a** showed the olefinic hydrogens as a singlet (δ 5.88) and the α-hydrogens as a doublet (δ 3.54) due to coupling (6 Hz) with the vicinal hydrogen. Structure **24a** was supported also by ir and elemental analysis. Alcohol **24a** gave an acetate **24b**, a 3,5-dinitrobenzoate **24c**, and a tosylate **6**. Attempts to crystallize **6** from pentane at 36° gave the rearranged *equatorial*-2-noradamantyl tosylate (**25**). (We omit the *equatorial*-designation because only *equatorial*-2-noradamantyl derivatives are involved here) Tosylate **6** also isomerized in carbon tetrachloride at 35 - 40° in the nmr probe (Scheme 4). We isolated tosylate **6** and recorded its nmr below 25° which showed **6** contained 15% of starting alcohol **24a**. 2-Noradamantyl tosylate (**25**) was obtained from the known alcohol, which was synthesized by sulfuric acid-ring opening of deltacyclane.[22] It was virtually free of *exo*-4-brendyl tosylate (< 2%).[22]

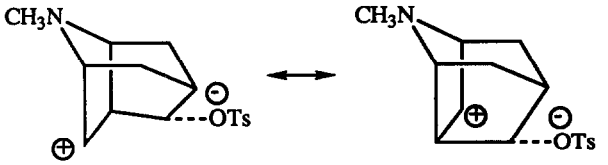
Kinetic Results. Solvolysis kinetics were conducted in 70% dioxane-water containing NaOH or $(i\text{-}Pr)_2NEt$; and rates were followed spectrophotometrically by measurement of the difference in absorbance of tosylate ester and tosylate anion. First-order kinetics were obeyed in all cases, and rate constants were calculated by York's least-squares computer program.[23] A fraction (*ca.* 15%) of both unsaturated tosylates **4** and **6** isomerized by internal return to unreactive tosylates, which did not perturb the linearity of the kinetic plots. The observed rate constant is the sum of solvolysis and isomerization rate constants ($k_{obs} = k_{solvolysis} + k_{isomerization}$). The fraction of isomerization in each run was calculated from the observed absorbance at zero and infinite times, and from the calculated absorbance assuming all starting tosylate had solvolyzed ($A_{\infty calc}$); $f_{isom} = (A_{\infty obs} - A_{\infty calc})/A_0 - A_{\infty calc})$. The rate of solvolysis of saturated tosylate **7** was estimated from the rate of the corresponding brosylate as reported by Sargent and Johnson[7].

The kinetic data at different temperatures are summarized in Table 1 along with fractions of isomerization and activation parameters. The temperature ranges are not wide, so the activation parameters are probably not precise. These parameters were used to estimate rates at 25°C for compounds **5** and **25**. Relative rate constants are presented in Table 2. We did not determine the *acetolysis* rate constant for carbocycle **6**, and Johnson and Sargent did not report data on **6** for *aqueous dioxane*. We estimated the relative acetolysis rate for tosylate **6** as follows: Noradamantyl brosylate should react *ca.* 3 times faster than noradamantyl tosylate **25**, i.e. $k_{OBs}/k_{OTs} \approx 3$ based on experience with other systems.[24]. We assumed that the rate ratio of **6** to **25** of 2700 in aqueous dioxane would also hold for acetolysis. Thus, the estimated acetolysis k_{rel} for **6/7** provides a rough estimate of the anchimeric assistance by the π bond in **6**. As is evident from Table 2 the ionization rate for the tropene tosylate **4** is 2×10^5 times that of the tropane tosylate **5**, and the rate for carbocyclic alkene **6** is almost 2×10^6 times the rate for the saturated heterocycle **5**. The known assistance factors for the sulfur mustard **1**,[2,3] the anti-7-norbornenyl **2**,[4] and the cyclopentenyl **3**[25] derivatives are 10^9, 10^{11} and 90, respectively. (It should be noted, however, that the saturated analog **2** also ionizes unusually slowly due to angle strain.) In this context, the assistance factors for **4** and **6** are substantial.

Heterocycle **4** reacts 8 times *slower* and not faster than carbocycle **6**. The simplest interpretation is that the amino group gives no rate enhancement beyond that provided by the double bond. Furthermore, the electronegative amino group should have a destabilizing inductive effect because it is β to two positive centers in

Table 1. Solvolysis in Dioxane—H_2O (70:30) Containing NaOH or $(i\text{-}Pr)_2NEt$

Compound	Temp °C	Buffer, (Number of Runs)	$10^4 k_{obs}$ sec^{-1}	Isomerization %	Activation Parameters
 4	25°	NaOH (3)	4.37 ± 0.04	17	$\Delta H^{\ddagger}$ = 18.9 kcal/mol
	35°	NaOH (3)	12.7 ± 0.2	15	$\Delta S^{\ddagger}$ = 10.5 eu
	25°	$(i\text{-}Pr)_2NEt$ (2)	3.8 ± 0.04	12	
 6	25°	NaOH (4)	35.0 ± 0.2	14.1	$\Delta H^{\ddagger}$ = 19.0 kcal/mol
	25°	$(i\text{-}Pr)_2NEt$ (2)	35.4 ± 0.4	12.7	$\Delta S^{\ddagger}$ = -6.0 eu
	13°	NaOH (2)	8.65 ± 0.1	19.7	
	13°	$(i\text{-}Pr)_2NEt$ (1)	9.1	12.3	
 5	90°	$(i\text{-}Pr)_2NEt$	0.37	0	$\Delta H^{\ddagger}$ = 31.7 kcal/mol
	100°	$(i\text{-}Pr)_2NEt$	1.24	0	$\Delta S^{\ddagger}$ = 8.1 eu
 25	65°	$(i\text{-}Pr)_2NEt$	1.67	0	$\Delta H^{\ddagger}$ = 23.7 kcal/mol
	75°	$(i\text{-}Pr)_2NEt$	4.75	0	$\Delta S^{\ddagger}$ = -5.9 eu



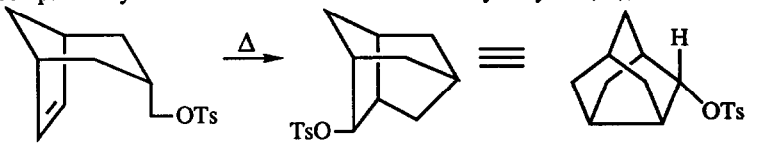
the transition state for ionization of **6**. Other researchers have estimated that inductive destabilization by a β-amino substituent diminishes rates by a factor of ten relative to hydrogen.[26a,b] Clearly, in the tropene system **4** our observed factor of 1/8 is understandable and is small compared to the π acceleration of 10^5.

Table 2. Relative Rates of Solvolysis of Tosylates at 25°C.

Compound	k_{rel} 70% Dioxane	k_{rel} Acetic Acid	Ref.
4	2.1×10^5		This work
5	1.0		This work
6	16.6×10^5	1.9×10^{5a}	This work
7	—	1.0[a]	7
25	614	70	This work

[a] *Estimated as described in the text.*

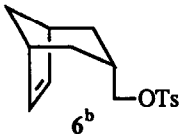
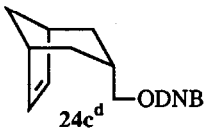
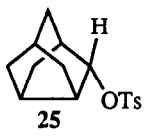
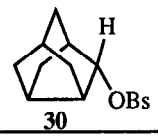
Solvolysis Products. Solvolysis of **6** in aqueous dioxane was rapid at 25° and gave 4-brendene (**26**), triaxane (**27**), *exo*-4-brendanol (**28**), and 2-noradamantanol (**29**) in a 0.7:3.4:3.4:92.5 ratio by gc (Table 3). Solvolysis was accompanied by 13% internal return to 2-noradamantyl tosylate (**25**), which was inert (2700-fold



6 **25** **25**

less reactive than **6**). 2-Noradamantanol (**29**) and *exo*-4-brendanol (**28**) were found in an average ratio of 96:4, and this agrees with the ratio 95:5 observed by Sargent and Johnson[7] for the solvolysis of unsaturated dinitrobenzoate **24c** in 70% aqueous acetone (Table 3). Our gc columns did not resolve alcohol **24a** from 2-noradamantanol (**29**). However, we used nmr as follows to exclude **24a** as a product of our solvolysis of the corresponding dinitrobenzoate **24c**. That ester (containing 2% alcohol **24a**) was solvolyzed in 90% CD_3COCD_3-10% D_2O. The α-hydrogen resonance of this 2% of **24a** did not change in intensity during the reaction. (Product ratios from gc were calculated after subtraction of the 2% contribution of starting alcohol **24a** to the 2-noradamantanol (**29**) peak.) 2-Noradamantyl tosylate (**25**) was solvolyzed at 65°C in 70% aqueous dioxane buffered with $(i\text{-}Pr)_2NEt$. The amine was used because sodium hydroxide in aqueous dioxane above 60° produced a polymeric material even in the absence of substrate. Tosylate **25** gave 4-brendene (**26**), triaxane (**27**), *exo*-4-brendanol (**28**), and noradamantanol (**29**) in almost identical ratios to those observed for unsaturated tosylate **6**. These product ratios also agreed with those observed independently by Kotcher, Huang, and Nickon[27] for acetolysis of 2-noradamantyl brosylate **30** (Table 3).

Table 3. Solvolysis Products from Carbocyclic Derivatives

Compound	Solvent	Buffer	T, °C	Products, Relative %[a] 26	27	28	29	Ref.
 **6**[b]	70% aq. dioxane	NaOH-NaCl	25°	0.7 (0.5)[c]	3.4 (3.0)[c]	3.4 (3.0)[c]	92.5 (80.5)[c]	This work
	70% aq. dioxane	NaOH-NaCl	25° (then 65°)[c]	0.2	2.2	2.6	95.0	This work
 **24c**[d]	90% aq. acetone	none	150°	-[e]	2.0	5.0	93.0	This work
	70% aq. acetone	urea	104°	-[e]	-[e]	5.0	95.0	7
 **25**	70% aq. dioxane	$(i\text{-Pr})_2$-NEt	65°	1.6	0.3	4.6	93.5	This work
 **30**	HOAc	urea	65°	-[e]	-[e]	4.5[f]	95.5[f]	27

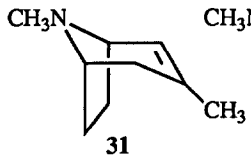
[a]From gc. [b]Tosylate contained 15% of corresponding alcohol **24a**, which was not resolved from **29** by gc. [c]Also a 13.4 ± 1% absolute yield of *equat*-2-noradamantyl tosylate (**25**) was formed by isomerization. Yield in parentheses calculated including 13% of **25** (See Scheme 4). In a second experiment the product mixture was heated to 65° to solvolyze **25**. [d]Dinitrobenzoate **24c** contained 2% of corresponding alcohol **24a** which was not a significant solvolysis product by nmr. [e]Detection not attempted. [f]Corresponding acetate was formed. See text.

Kinetic and product studies of the saturated 3α-hydroxymethyltropane tosylate (**5**) were complicated by the formation of a yellow, UV-absorbing substance. This disturbance was much more serious with sodium hydroxide than with diisopropylethylamine. The products (summarized in Table 4A) were alkenes **31** and **32** and alcohols **33** and **34**. Independently we prepared the first three by known routes for direct comparison by ir, nmr, and gc. Tertiary alcohol **34** was identified solely from its spectral properties. The material recovery was only 76%. At least a portion and perhaps all of the unaccounted starting tosylate must be responsible for the yellow, UV-absorbing material. The product distribution from solvolysis of unsaturated tropene tosylate **4** determined by nmr and gc are shown in Table 4B. Our structural assignments of **35**, **36** (a carbinolamine) and **37** are tentative, but they are strongly supported by ir, nmr, and analytical data. The proposed structures are based on analogy to products from unsaturated carbocyclic tosylate **6**, although the proportions are quite different in the two cases. Structures for the two unknown tosylates could not be ascertained.

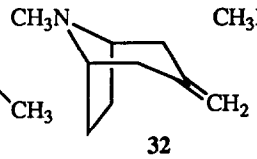
Summary of Kinetic and Product Studies. A plausible accounting of the products of solvolysis of **6** in aqueous dioxane is summarized in Scheme 4. Tosylate **6** ionizes with double bond participation to ion pair **38**, which can collapse by internal return to noradamantyl tosylate (**25**). Ion pair **38** can also give triaxane (**27**) by proton loss and noradamantanol (**29**). Competitive rearrangement of ion **38** to ion **39** (or its classical counterpart)

Table 4. Solvolysis Products from Heterocyclic Derivatives

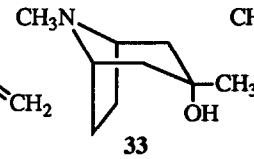
A. 3α-Hydroxymethyltropane Tosylate (**5**) in 70% Dioxane-0.045 M NaOH at 100°C.



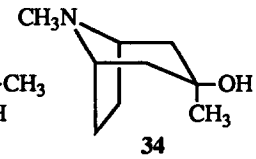
31 20%



32 37%



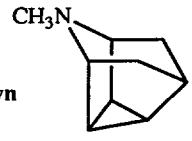
33 9%



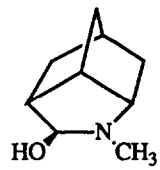
34 10%

B. 3-α-Hydroxymethyltrop-6-ene Tosylate (**4**) in 70% Aqueous Dioxane-0.03 M NaOH at 25°C

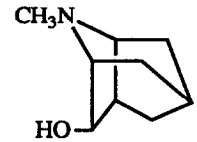
Two unknown tosylates 17%



35 25%



36 41%



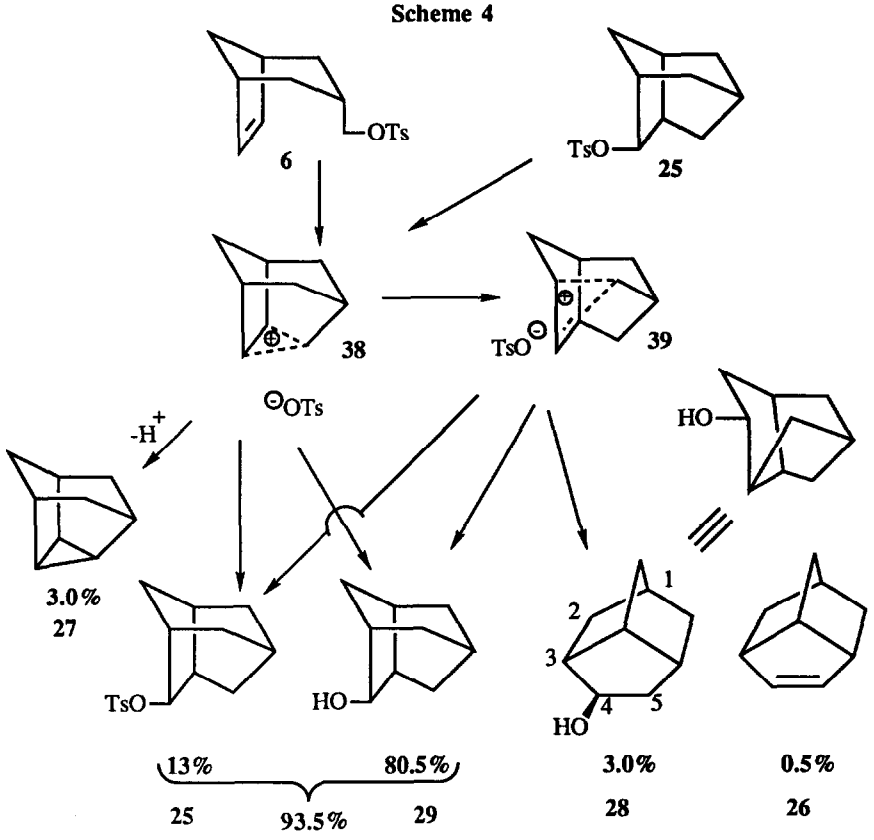
37 17%

would account for 4-exo-brendanol (**28**) and 4-brendene (**26**). Competitive rearrangement of ion **38** to ion **39** (or its classical counterpart) would account for 4-exo-brendanol (**28**) and 4-brendene (**26**). Ion **39** probably cannot form directly by ionization of **6**, because double bond participation presumably involves both alkene carbons simultaneously as is known for the 2-(Δ^3-cyclopentenyl)-ethyl system 3.[25] Furthermore, at 25° **39** cannot arise from **6** *via* **25** because tosylate **25**. To a first approximation, all the substrates in Table 3 gave remarkably similar product mixtures which suggest a common intermediate **38** leading predominantly to **29**. A small portion of **38** is diverted to **39**, but this interconversion likely does not represent an actual equilibration of ions **38** and **39** because

independent studies on acetolysis of 4-exo-brendyl brosylate (the ester of **28**)[27b] gave a quite different product mixture than those from **6**, **25** and **30** (Table 3).

The products from reference saturated tosylate **5** (Table 4A) can be rationalized on the basis of direct formation of a tertiary cation, perhaps by hydrogen assisted ionization of the primary tosylate. About half of this ion undergoes elimination to alkenes **31** and **32** and the remainder captures nucleophile to give alcohols **33** and **34**. The yield of exo alkene **32** appears to us to be unusually high (compared to **31**), and **32** may arise by an internal,

Scheme 4



amino-promoted E-2 elimination from the boat form of **5**. The major products **35**, **36**, and **37** from the tropene tosylate **4** (Table 4B; tentative assignments), correspond to the three structural types that arose from unsaturated carbocycle **6** but in markedly different proportions. Evidently, the methylamino substitutent diverts the bulk of the 2-noradamantanol skeleton to the "azatriaxane" **35** (25%) and the "azabrendanol" **36** (41%). The bias toward **36** probably reflects stabilization of its cation precursor by resonance interaction with nitrogen. It seems unlikely that this cation would form a stable tosylate product by internal return; however, one of the two "unknown tosylates" may well correspond to **37**.

Experimental

General. M-H-W Laboratories, Garden City, Michigan performed all elemental analyses. All melting points were taken in Pyrex capillaries and are corrected. Baker "Analyzed" benzene was used for extractions. The highest quality reagents and solvents were purchased from Baker, Eastman or Aldrich and used as received unless otherwise noted. Dry DMSO for small scale experiments was distilled from CaH_2 as needed. Reagent THF was distilled from $LiAlH_4$ under nitrogen and dry pyridine was distilled from CaH_2. Technical grade pentane was purified by a standard procedure.[28] Infrared spectra were recorded on a double-beam grating spectrophotometer in NaCl or Irtran-2 cells. Band positions are given in reciprocal centimeters and the cm^{-1} is omitted. Ultraviolet spectra and kinetics were carried out on a Cary Model 14 Spectrophotometer as described below. Proton magnetic resonance spectra were recorded on Varian Model A-60 or Model HA-100 Spectrometers, or on a JEOL Model MH-100 Spectrometer. Chemical shifts are δ units downfield from internal tetramethylsilane (TMS), followed by the multiplicity, number of hydrogens and the assignment. Mass spectra (ms) were recorded on a Hitachi-Perkin-Elmer Model RMU-6 Mass Spectrometer. Peaks are reported as m/e ratios followed by relative intensities in parentheses. Analytical gc[29] was done with a Perkin-Elmer Model 900 Gas Chomatograph equipped with a flame ionization detector. Preparative gc[29] was performed with a Varian Aerograph "Autoprep" Model A-700 equipped with a thermal conductivity detector. Helium carrier gas was used in all cases.

Tropan-3-one (9) was kindly supplied by Dr. M. Tischler of Merck and Co.

3-Methylenetropane (10). A 100-mL flask with side arm, stirring bar, N_2 inlet, and serum stopper was charged with potassium *tert*-butoxide (t-BuOK) (2.033 g, 18.11 mmol, sublimed) and methyltriphenylphosphonium bromide (6.72 g, 18.81 mmol). It was cooled to 0° under dry nitrogen, and dry THF (30 mL) was added *via* syringe. The ylide solution was stirred 20 min. Pure tropan-3-one (2.00 g, 14.36 mmol, mp 42-43°) in dry THF (5 mL) was added *via* syringe at 0° and the solution was stirred 50 min at 25° and quenched with H_2O (2 mL). The mixture was acidified and THF was removed *in vacuo* at 30°. The residue was diluted with H_2O and Ph_3PO was extracted with benzene. The aqueous solution was basified (K_2CO_3), and extracted thrice with pentane. The dried extracts were concentrated under aspiration, and the residual liquid was distilled at 25° (0.05 mm) into a Dry Ice trap. The liquid distillate (1.84 g) was 3-methylenetropane (r.t. 3.2 min) with pentane (r.t. 0.4 min, 8%) as the only impurity by gc (A-5, 90°, 20 psi).[29] The yield was *ca.* 1.69 g (86%) after allowance for the pentane. Pure 3-methylenetropane was obtained as a clear liquid by preparative gc (P-1, 80°, 11 psi, r.t. 16 min).[29] Nmr (CCl_4) 4.65 (t, J = 2, 2, = CH_2), 3.05 (pseudoquartet, $W_{1/2}$ = 9 Hz, 2, bridgeheads), 2.45 (broad d, J = 13, 2) 2.24 (s, 3H NCH_3), 2.0-1.85 (complex, 6).

Anal. Calcd for $C_9H_{15}N$: C, 78.77, H, 11.02. Found: C, 79.08; H, 11.23.

Tropan-6β-ol-3-one (13) was prepared by a known procedure[11] as modified [30] from 26 g (0.2 mol) of 2,5-dimethoxy-2,5-dihydrofuran. Our yield was 20-30% whereas theirs was 35-40%. Recrystallization from ethanol-hexane gave tropan-6β-ol-3-one as white crystals (9.28 g, 30%); mp 121 - 122.0, lit.[30] 122.5° - 123.5°; ir ($CHCl_3$) 3585 - 3400 (OH), 1710 (vs, C = O); nmr ($CDCl_3$) 4.9 (t, J = 5, 1, α–H), 3.52 (m with s at 3.48, 3, bridgeheads and OH), 2.66 (s, 3, NCH_3), 2.9-1.9 (complex, 6).

Tropan-6β-ol-3-one Acetate (17) was prepared with Ac_2O/Py by the procedure of Stoll, *et al.*[31] Bulb to bulb distllation gave a clear oil (4.98 g, 97%) that was crystallized from ether-hexane. Tropan-6β-ol-3-one acetate (4.11 g, 80%) was obtained as oily crystals, mp 46 - 47.5°; lit.[31] 51 - 52°.

3-Methylenetropan-6β-ol Acetate (18). This substance was prepared from methyltriphenylphosphonium bromide (2.43 g, 6.8 mmol) t-BuOK (726 mg, 6.5 mmol, sublimed) and tropan-6β-ol-3-one acetate (17) (778 mg, 3.9 mmol) as described above for 3-methylene tropane (10). The dried pentane extract was evaporated without heat, and the residual liquid was distilled at 80° (0.05 mm) into a Dry-Ice-cooled trap. Gc of the neat distillate (A-5, 140°, 10 psi)[29] showed an impurity (r.t. 10 min, 1.6%) and 3-methylenetropan-6β-ol acetate (r.t. 1.4 min, 98.4%); 646 mg (85%). Preparative gc (P-2, 130°, 20 psi)[29] gave the pure acetate (r.t. 10.5 min); ir (CCl_4), 1735 (vs, C = O); nmr ($CDCl_3$) 4.99 (d of d, J = 6, J = 5 , 1, α-H), 4.70 (q, J = 2, 2 = CH_2), 3.28 (m, $W_{1/2}$ = 26 Hz, 2, bridgeheads), 2.57 (s, 3, NCH_3), 2.05 (s, 3, CH_3CO_2-), 2.8-1.6 (complex, 6). Distillation at 129° (12 mm) gave the analytical sample.

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.54; H, 8.90; N, 7.42.

3-Methylenetropan-6β-ol (14). A. By Saponification of 3-Methylene-tropan-6β-ol Acetate. After standing at 25° for 12 h, a solution of 3-methylenetropan-6β-ol acetate in 0.18 N NaOH was saturated with K_2CO_3 with cooling. The mixture was extracted with ether (4 x 20 mL), and the dried ($MgSO_4$) combined extract was concentrated *in vacuo* to an oil (602 mg). Gc (A-5, 100°, at 10 psi)[29] showed one peak with coincidentally the same retention time as starting acetate (r.t. 6.0 min). Spectral data indicated no residual starting acetate: ir (CCl_4) 3610 - 3420 (OH), no C = O; nmr (CCl_4) 4.70 (sharp m, 2, = CH_2), 4.57 (s, 1, OH), 3.99 (d of d, J = 6 and 4, 1, α-H), 3.31 (m, 1, bridgehead), 3.01 (m, 1, bridgehead), 2.53 (s, 3, NCH_3), 2.8 - 1.5 (complex, 6). Crystals were obtained from pentane (570 mg, 89%), mp 47-49°. Two recrystallizations and a sublimation at 40° (0.05 mm) gave the analytical sample, mp 46 - 48°.

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.47; H, 10.10; N, 9.19.

B. By Wittig Reaction with Tropan-6β-ol-3-one. Potassium *tert*-butoxide (5.42 g, 48.3 mmol) and methyltriphenylphosphonium bromide (17.86 g, 55 mmol) were stirred at 0° under argon in THF (50 mL). The solution was stirred for 15 min before tropan-6β-ol-3-one (**13**) (5.00 g, 32.2 mmol, mp 121 - 122°) in dry THF (220 mL) was added dropwise. The solution was stirred at 0° for 1.5 h and at 25° for 4 h. The mixture was quenched with H_2O (30 mL) and worked up as above. The dried pentane solution was concentrated to an oil (4.54 g, 92%) that crystallized from pentane when cooled to -78°, and then at 0°. This procedure gave white crystals (4.04 g, 82%, mp 47-49°). Ir (CS_2) 3612 - 3430 (w, OH). Nmr (CCl_4) showed 4.62 (m, 2, = CH_2), 4.12 (broad s, 1, OH), 3.88 (d of d, J = 7 and 3.5, 1, α–H), 3.24 (m, $W_{1/2}$ = 12 Hz, 1, C - 1 bridgehead), 2.94 (pseudotriplet, J = 2.5, 1, C - 5 bridgehead), 2.46 (s, 3, NCH_3), 2.6 - 1.6 (complex, 6).

3-Methylenetropan-6β-ol Tosylate (15). A. Pyridine Method. A solution of 3-methylenetropan-6β-ol (**13**) (450 mg, 2.94 mmol, mp 45 - 47.5°) in dry pyridine was cooled to 0°, and tosyl chloride (1.12 g, 5.9 mmol, mp 67-68.5°) was added. The solution was stored at 0° for 27 h before 10% Na_2CO_3 (25 mL) was added. The mixture was extracted with CH_2Cl_2 and the dried extracts were concentrated on the rotary evaporator. Pyridine was evaporated at 25° (0.05 mm), and the yellow oil (711 mg, 78% if pure) was dissolved in ether and treated with activated charcoal. A solid was obtained after aspiration. Two recrystallizations from pentane gave pure 3-methylenetropan-6β-ol tosylate (**15**) (414 mg, 46%); mp 82 - 83°; the ir was in accord with the assigned structure; nmr (CCl_4), 7.81 and 7.38 (AB d, J = 8.5, 4, arom H), 4.75 (complex m, 3, α-H and = CH_2), 3.27 (m, 2, bridgeheads), 2.46 and 2.43 (s, s, 6, $PhCH_3$ and NCH_3), 2.6 - 1.6 (complex, *ca.* 6).

Anal. Calcd for $C_{16}H_{21}NO_3S$: C, 62.51; H, 6.89; N, 4.56; S, 10.43. Found: C, 62.61; H, 6.93; N, 4.47; S, 10.27.

B. *n*-Butyl Lithium Method. A solution of 3-methylenetropan-6β-ol (4.03 g, 26.3 mmol, mp 46 - 47.5°) and triphenylmethane (2 mg) in dry THF (20 mL) was stirred at 0° under nitrogen as 2.2 M *n*-BuLi in hexane was added from a syringe until the solution became slightly pink. The precipitated lithium alkoxide, was stirred 10 min at 0° before tosyl chloride (5.01 g, 26.3 mmol) in THF was added dropwise. The solution was stirred 2.5 h at 0°, diluted with ether and washed with saturated NaCl. The ether was concentrated to a solid (8.09 g, 100%). The tosylate (**15**) was recrystallized for ether pentane to give pure tosylate (7.14 g, mp 82 - 83.5°). The mother liquors afforded another crop (0.44 g, mp 80 - 82°). The ir and the nmr spectra were in agreement with samples prepared by Method A.

3-Methylenetrop-6-ene (16). A solution of 3-methylenetrop-6β-ol tosylate (1.00 g, 3.25 mmol, mp 82.5 - 83.5°) in dry DMSO (3 mL) was stirred at room temperature under N_2 as a solution of t-BuOK (0.729 g, 6.5 mmol, sublimed) in dry DMSO (10 mL) was added dropwise. The opaque blue solution was stirred 10 min, diluted with H_2O, saturated with NaCl, and extracted with pentane. The pentane extract was washed with saturated NaCl dried over $MgSO_4$, and concentrated to an oil (420 mg, 95%) that was shown by gc (A-3, 80°, 20 psi, neat injection)[29] to be 99% pure (r.t. 7.5 min, several trace impurities r.t. *ca.* 0.6 min). Preparative gc (P - 1, 95°, 14 psi) of the diene (347 mg, r.t. 12 min) gave a clear liquid that was pure by gc; ir (neat) was in accord with the proposed structure; nmr (CCl_4) 5.74 (s, 2, CH = CH), 4.52 (t, J = 2, 2, = CH_2), 3.33 (pseudotriplet, 2,

bridgeheads), 2.46 and 1.96 (AB d, J = 14, 4, C - 2 and C - 4 H), 2.10 (s, 3, NCH_3). Bulb to bulb distillation at 100° (15 mm), bp 140° at 760 mm, gave the analytical sample.

Anal. Calcd for $C_9H_{13}N$: C, 79.95; H, 9.69; N, 10.36. Found: C, 80.07; H, 9.82; N, 10.62.

3α-Hydroxymethyltropan-6β-ol 6-Tosylate (19). A solution of disiamylborane[8] was prepared by addition of 1.67 M "BH_3" in THF (170.1 mL, 284.0 mmol) to stirred 2-methyl-2-butene (39.85 g, 60.2 mL, 568.1 mmol) at 0° under nitrogen. The solution was stirred 1 h at 0° before addition of 3-methylenetropan-6β-ol tosylate (**15**) (21.83 g, 71.01 mmol, mp 82 - 83.5°) in dry THF (150 mL). After 30 min at 0° and 3.5 h at 25° the borane was quenched by *careful* addition of H_2O. Methanol (150 mL) and 3 N NaOH (95 mL, 285 mmol) were added. The stirred solution was oxidized at 0° by 30% H_2O_2 (55.2 mL, 639 mmol, 11.6 M) added dropwise over 30 min. The reaction was neutralized with HCl and the solvent was evaporated. The residue was taken up in ether. Evaporation gave a viscous oil (24.78 g, 100%); ir ($CHCl_3$) 3605, 3400 (OH), 1360 (m, $\nu_{as}SO_2$), 1192 and 1177 (m, and vs, ν_s SO_2), 1030 (w, C - O). The nmr showed no detectable olefinic hydrogen resonance (4.68, m) of the starting material; 7.76 and 7.32 (AB d, J = 8, 4, aromatic H), 4.96 (d of d, J = 6.5 and 4, 1, tosylate α–H), 3.40 distorted d, J = 3.7, expected 3, alcohol OH and α–H), 3.20 (m, *ca.* 2, bridgeheads), 2.42 and 2.39 (s, s, 6, $PhCH_3$ and NCH_3), 2.3 - 1.1 (complex, 8, expected 7). The oil would not crystallize after repeated trials and no elemental analysis was obtained.

3α-Hydroxymethyltropan-6β-ol 3-Acetate 6-Tosylate (17). A solution of crude 3α-hydroxymethyltropan-6β-ol 6-tosylate (19) (171 mg, 0.525 mmol) and acetic anhydride (2.5 mL) in dry pyridine (2 mL) stood at 25° for 12 h. Work up gave a clear oil (146 mg, 76%) that would not crystallize; ir (CCl_4) 1740 (vs, C = O of acetate); nmr ($CDCl_3$) 7.88 and 7.45 (AB d, J = 8 , 4, arom H), 5.06 (d of d, J = 6.5 and 4.5, 1, CHOTs), 3.95 (d, J = 7, 2, CH_2OAc), 3.34 (m, $W_{1/2}$ = 8 Hz, 2, bridgeheads), 2.48 (s, 6, NCH_3 and $PhCH_3$), 2.07 (s, ca. 3, CH_3CO_2 -), 2.4 - 0.8 (complex, *ca.* 10, expected 7). The product was impure.

9-Methyl-9-aza-4-oxatricyclo[4.3.1.0^{3,8}]decane (18). Crude acetate tosylate **17** (51 mg, 0.139 mmol) was dissolved in DMSO-d_6 (0.25 mL) in an nmr tube with TMS and the spectrum was recorded: 7.9 and 7.6 (AB d, J = 8 Hz, 2, Ar-H Hs), 4.98 (t J = 5 Hz, 1, CHOTS), 3.91 (d, 6 Hz, 2, CH_2OAc), 2.03 (s, *ca.* 3, CH_3CO_2). Potassium *tert*-butoxide (165 mg, 1.47 mmol, sublimed) was added. In 3 min the nmr showed aromatic H's of tosylate anion. No acetate CH_3 at 2.03, and two new α-H resonances at 4.7 (pseudotriplet, J = *ca.* 7.5 Hz) and 3.78 (sharp m). After quenching, extractive workup, drying, and concentration we obtained a clear liquid (13.7 mg, 65%), ir (CCl_4) 1102 (s, C-O-C); nmr (CCl_4) 4.56 (pseudotriplet, J = *ca.* 7 Hz, 1, 3° α-H), 3.78 (sharp m, 2, -CH_2-O-), 3.06 (broad m, $W_{1/2}$ = 22 Hz, 2, bridgeheads), 2.27 (s, 3, NCH_3) 2.5—1 (complex, 8, expected 7). The spectral data are consistent with the proposed structure **18.**

3α-Hydroxymethyltropan-6β-ol 6-Tosylate Tetrahydropyranyl Ether (19). A solution of 3α-hydroxymethyltropan-6β-ol 6-tosylate (**19**) (24.78 g, 76.15 mmol) in purified dihydropyran[28] (300 mL) was stirred at 0° in a flask equipped with a drying tube and thermometer. Solid TsOH·H_2O (15.47 g, 81.34 mmol, 6% excess) was added in small portions during 1.5 h to keep the temperature below 2°. When the acid had dissolved, the solution was stirred 2.5 h at 0° and concentrated to *ca.* one-half volume under aspirator vacuum at 25°. If the temperature reached 25° before all the tosic acid had dissolved or before the reaction was complete a ***violent exothermic polymerization*** occurred and a black tar formed. The dihydropyran solution was diluted with pentane (2L), and allowed to stand for 2 h. The pentane was decanted from the ammonium salt, which was washed with pentane and triturated with 15% NaOH (50 mL). The residue was extracted with ether and the ether solution was dried and concentrated to an oil (31.15 g, 99%); nmr (CCl_4), 7.81 and 7.37 (AB d, J = 8, 2, arom H), 5.01 (d of d, J = 12 and 6, 1, CHOTs), 4.54 (m, 1, acetal H), 4 - 3.2 (m, *ca.* 4, CH_2O groups), 3.15 (m, *ca.* 3, expected 2, bridgeheads), 2.47 and 2.38 (2s, *ca.* 6, NCH_3 and $PhCH_3$), 2.2 - 1.2 (complex, *ca.* 13).

3α-Hydroxymethyltrop-6-ene Tetrahydropyranyl Ether (20). A solution of crude 3α-hydroxymethyltropan-6β-ol 6-tosylate tetrahydropyranyl ether (31.15 g, *ca.* 76.15 mmol) in dry DMSO (130 mL) was stirred at 25° under nitrogen as a solution of potassium t-BuOK (17.09 g, 152.3 mmol) in dry DMSO (50 mL) was added dropwise with cooling. The solution was pured onto ice (600 g) and 50% NaCl (1.4 L). Pentane extraction and concentration gave an impure oil (24.67 g, expected 18.07 g). This material was used for the next step without purification. A portion was purified by preparative gc (P-3, 160°, 10 psi)[29] to give a clear liquid (99% pure by gc); nmr (CCl_4) 5.84 (s, 2, olefin H), 4.41 (m, 1, acetal H), 3.8 - 3.04 (complex with sharp m at

3.25, 6, CH_2 - O groups and bridgeheads), 2.13 (s, 3, NCH_3), 2.1 - 1.2 (complex, 11). Distillation at 94° (0.05 mm) afforded the analytical sample.

Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.90; H, 9.73; N, 6.01.

3a-Hydroxymethyltrop-6-ene (21). Crude 3α-hydroxymethyltrop-6-ene tetra hydropyranyl ether (9.09 g, *ca.* 73% pure, or *ca.* 6.67 g of pure acetal, 28 mmol) was dissolved in 281 mL of 0.1 N HCl in methanol for 45 min. The methanol was removed *in vacuo*. The salt was washed with ether, dried and triturated with 50% K_2CO_3. The mixture was extracted with ether. The extracts were dried, treated with charcoal, filtered, and concentrated to an oil (4.36 g, *ca.* 100%). Crystals were obtained at -20° from ether-pentane. Two recrystallizations from ether gave prisms of **23**, mp 71.5 - 72°. On gc (A-3, 100°, 10 psi) the alcohol (r.t. 10.6 min) showed no impurities; ir (CS_2) 3610, 3500 - 3050 (OH); nmr ($CDCl_3$) 5.94 (s, 2, olefin H), 3.55 (d, J = 7.5, 2, α–H), 3.41 (m, 2, bridgeheads), 2.49 (s, 1, OH), 2.26 (s, 3, NCH_3), 2.2 - 1.3 (complex, 5). The mass spectrum (70 eV) showed 153 (6, M^+) 136 (4.6, M - 17), and 94 (100, $C_6H_8N^+$).

Anal. Calcd for $C_9H_{15}NO$; C, 70.55; H, 9.87; N, 9.14. Found: C, 70.18; H, 10.10; N, 9.11.

Hydrogenation of 3α-Hydroxymethyltrop-6-ene (21) to 3α-hydroxymethyltropane. 3α-Hydroxymethyltrop-6-ene (10.4 mg, 0.067 mmol, mp 66 - 70°) in CH_3OH (10 mL) was hydrogenated at room temperature for 2.5 h over 10% Pd on charcoal (3 mg) at 43 - 26 psi in a Parr low-pressure hydrogenation apparatus. Work-up afforded a sample identical to authentic 3α-hydroxymethyltropane (**11**) (mp 70 - 74°). The oil (3.9 mg) crystallized from ether-pentane affording needles (1.7 mg), mp 74.5 - 75.5°.[9]

3α-Hydroxymethyltrop-6-ene Tosylate (5) was prepared by the Method B described above (2.84 g, 89%); nmr ($CDCl_3$) 7.82 and 7.40 (AB d, J = 8, 4, tosylate aromatic H), 5.85 (sharp m, 2, olefin H), 4.03 (d, J = 7.5, 2, α–H), 3.38 (m, 2, bridgeheads), 2.46 (s, 3, $PhCH_3$), 2.25 (s, 3, NCH_3), 2.2 - 1.0 (complex, 6, expected 5). The tosylate crystallized from ether-pentane at -78° but melted at room temperature. A solution of the amino tosylate (**5**) (1.68 g, 5.46 mmol) in anhydrous ether (65 mL)was saturated with HCl gas. Ether was evaporated; and the residual salt was washed twice with ether. The salt was recrystallized from ether methanol. Two recrystallizations gave the pure HCl salt (1.66 g, 88%), mp 142 - 143°; nmr ($CDCl_3$) 7.73 and 7.36 (AB d, J = 8, 4, aromatic H), 6.08 (s, 2, CH = CH), 4.09 (sharp m, 2, bridgeheads), 4.01 (d, J = 7, 2, α–H), 2.80 (broad s on m, 5, CH_3NH^+ and C - 3 H?), 2.43 (s, 3, $PhCH_3$), 2.4 - 2 (complex, 2), 1.67 (d, J = 14, 2).

Anal. Calcd for $C_{16}H_{22}ClNO_3S$: C, 55.89; H, 6.45; Cl, 10.31; N, 4.07; S, 9.36. Found: C, 55.97; H, 6.48; Cl, 10.25; N, 4.28; S, 9.03.

3,4-Dibromobicyclo[3.2.1]octa-2, 6-diene was prepared by the method of Moore, *et al.* except on twice the scale.[20] Also we exercised care in the distillation that otherwise led to extensive isomerization. Our yield of bromide was 55%, vs 35% reported[20] and it was converted to 3-bromobicyclo[3.2.1]octa-2,6-diene (**22**) as described.[20] 3-Carboxybicyclo[3.2.1]octa-2,6-diene was prepared as described.[18,19] The nmr agreed with Fogelsong's: 11.74 (s, 1, OH), 7.48 (d, J = 7, 2, C-2H), 7.12 and 7.78 (d of q, J = 7 and 3, 2, C-6 and C-7 H), 3.1 - 1.4 (complex, 6.7, expected 6). The yield was 30.9 g (76% crude), mp 135 - 143°, lit.[19] 143 - 145°. This crude material was used in the next step.

3α-Carboxybicyclo[3.2.1]oct-6-ene (23) was prepared by reduction of the carboxylic acid from **22** with sodium in liquid ammonia and quenching with t-BuOH instead of i-PrOH to increase the fraction of the 3α-carboxylic acid (**23**). The ratio of 3α to 3β-epimers was 2.4:1 compared to *ca.* 1:1 for iso-PrOH. The 3 α-acid was converted to its iodo lactone[19] and the 3β-acid was base extracted. Purification gave 493 mg (85%) of the β-epimer mp 112 - 119, lit.,[19] 121 - 123°. The iodo lactone was converted to 3α-carboxybicyclo-[3.2.1]oct-6-ene with Zn/HOAc.[21] The material (74%) mp 141 - 144°, lit.,[19] 145 - 146° gave the reported spectral properties. This substance was reduced with $LiAlH_4$. Two recrystallizations gave 3α-hydroxmethylbicyclo[3.2.1]oct-6-ene (**24**) mp 40-41°.[19]

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.05; H 10.03.

3α-Hydroxymethylbicyclo[3.2.1]oct-6-ene acetate (24b) was formed as an oil by the usual pyridine-acetic anhydride method in 93% yield; nmr (CCl_4) 5.90 (s, 2, CH = CH), 3.93 (d, J = 7.5, 2, CH_2O), 2.5 (m, 2, bridgeheads), 1.89 (s, CH_3CO_2) and 2.2 - 1.2 (complex, 10).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.15; H. 8.85.

3α-Hydroxymethylbicyclo[3.2.1]oct-6-ene 3,5-Dinitrobenzoate (24c) was synthesized in pyridine from the acid chloride in 97% crude yield. Two crystallizations gave an analytical sample, mp 110 - 112°.

Anal. Calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43. Found: C, 57.88, H, 4.88; N, 8.34.

2-Noradamantanol Tosylate (25). Noradamantanol prepared in our laboratory by P. Kotcher by a known procedure[22] was converted to the tosylate by Method B above, and recrystallized from pentane at 0°. Spectral properties agreed with reported data.[22]

Anal. Calcd for $C_{16}H_{20}SO_3$: C, 65.72; H, 6.89; S, 10.97. Found: C, 65.91; H, 7.08; S, 10.81°.

Solvolysis Products. 3α-Hydroxymethylbicyclo[3.2.1]-6-ene Tosylate (6) in 70% Aqueous Dioxane-0.02 M NaOH. This tosylate contained 15% of (**24a**) as the only impurity detectable by nmr. A 1.8 mL aliquot of the stored ether solution of the tosylate was concentrated under vacuum to a clear oil (80 mg, 0.27 mmol) that was immediately dissolved in 30 mL of 70% aqueous dioxane-0.02 M NaOH. After 40 min (12 half-lives) at 25° one-half of the solution was heated in a sealed tube under argon at 64.6° for 16.5 h (13 half-lives) to solvolyze 2-noradamantyl tosylate (from internal return). The other half was diluted with H_2O, extracted with ether, and concentrated to 5-mL. Gas chomatography (A-1, 150°, 30 psi)[29] showed exo-4-brendanol (r.t. 21 min, 3.4%) and 2-noradamantanol (r.t. 24.7 min, 92.6%) as well as an unidentified peak (r.t. 31.4 min, 4%). We conclude that (**24a**), which is not resolved from 2-noradamantanol under the gc conditions, was not a product because solvolysis of the corresponding dinitrobenzoate gave no uncyclized, olefinic alcohol. Eighty-five percent of the major gc peak was used as the basis to calculate the relative yield of 2-noradamantanol in the product mixture because 15% of this peak was due to **24a**. The average ratio of 2-noradamantanol (**29**) to *exo*-4-brendanol (**28**) was 96.5:3.5. On gc column A-2, (90°, 50 psi), 4-brendene (r.t. 16.6 min) and triaxane (r.t. 21.4 min) were resolved in a 1:5 ratio, with the triaxane peak roughly the same area as the *exo*-4-brendanol peak. 4-Brendene (**26**), triaxane (**27**), *exo*-4-brendanol (**28**), and 2-noradamantanol (**29**) were produced in a ratio of *ca.* 0.7:3.4:3.4:92.5, respectively. The kinetic experiments provided a 13.4% yield of **25**. The second solvolysis aliquot was extracted with pentane and concentrated to 5 mL. Gas chomatography as described above (A-1, 155°, 30 psi) showed a 3:97 ratio of *exo*-4-brendanol to 2-noradamantanol. On the second column (A-2, 100°, 50 psi) 4-brendene and triaxane were detected. After temperature programming to 170°, we observed peaks for *exo*-4-brendanol (2.6%) and 2-noradamantanol (95%). Product ratios were calculated after allowance for the 15% of **24a** in the starting tosylate (Table 3). The product composition was confirmed the by conversion of the product to acetates. The mixture was analyzed on a 450-ft Golay R column (A-10, 125°, 60 psi) capable of resolving the acetates. The only acetates detected were *exo*-4-brendyl (2%), 2-noradamantyl (90%), and 3α-hydroxymethylbicyclo-[3.2.1]oct-6-ene acetate (8%); and the limit of detection was 0.05%.

Products from 2-Noradamantyl Tosylate (25) at 64.6° in 70% Aqueous Dioxane-0.02 M Diisopropylethylamine. Analysis by gc (A-1, 155°, 30 psi) showed a 5:95 ratio of *exo*-4-brendanol (**28**) and 2-noradamantanol (**29**). Analysis on another column (A-2, 100°, 50 psi) showed 4-brendene (**26**), Table 3.

Products of Solvolysis of 3α-Hydroxymethyltropane Tosylate (5) in 70% Aqueous Dioxane—0.045 M NaOH. Pure 3α-hydroxymethyltropane tosylate (186 mg, 0.6 mmol, mp 41-42°) was solvolyzed in 70% aqueous dioxane-(0.045 M NaOH), in a sealed tube under argon at 105° for 82.5 h. The yellow solution (pH 11.7) was acidified to pH 6.5. Solvent was evaporated and the residual HCl salts were treated with 50% K_2CO_3. The mixture was extracted with ether, and the dried extracts were concentrated (63.2 mg, 76%). The nmr ($CDCl_3$) of the crude product showed 3-methyltrop-2-ene (**31**) (5.46, = CH -; 2.30 NCH_3) and 3-methylenetropane (**32**) (4.70, = CH_2; 3.33, NCH_3) as the major products in a 35:65 ratio, respectively *via* olefinic H integration. No tosylate aromatic hydrogens were observed Gc (A-3, 70°, 10 psi) gave an 86:6:8 ratio of total amino olefins (**31** and **33**, r.t. 5.2 min, olefins not resolved) to 3α-alcohol (**33**) (r.t. 18.2 min) to 3β-alcohol (**34**) (r.t. 23.4 min). Preparative gc (P-3, 80°, 8 psi) of the crude product mixture did not separate the tertiary alcohols, which were

collected in one fraction (5 mg). The nmr (CCl_4) of this mixture was consistent with *ca.* a 1:1 mixture of 3β-methyltropan-3α-ol (**33**) and 3α-methyltropan-3β-ol (**34**): 4.00 (broad s, 1, OH), 3.20 and 3.04 (m and m, 2, bridgeheads), 2.26 and 2.22 (s and s, *ca.* 3, NCH_3's), 2.2 - 1.2 (complex, 9, expect 8), 1.13 and 1.10 (s and s, 3, C-CH_3). Authentic 3α-methyltropan-3β-ol was not prepared, but its presence in the solvolysis product mixture was deduced from the spectral data. A second preparative solvolysis was examined by gc (A-3, 80° for 16 min and 10°/min to 120°, 10 psi). A 90:5:5 ratio of amino olefins (r.t. 3.0 min, olefins not resolved) to 3β-methyltropan-3α-ol (r.t. 10.5 min) to 3α-methyltropan-3β-ol (r.t. 13.7 min) was observed. A trace of 3α-hydroxymethyltropane (< 1%, r.t. 23.4 min) was observed and was confirmed by peak enhancement with an authentic sample. The gc yield of amino olefins was *ca.* 50%. The material balance was 76%. Presumably the missing material is responsible for the spectral disturbances in the kinetic experiments.

Preparative Solvolysis of 3α-Hydroxymethyltrop-6-ene Tosylate (4) in 70% Aqueous Dioxane Containing 0.03 M NaOH. Pure tosylate hydrochloride (40 mg, 0.116 mmol) was solvolyzed at 25° in 70% aqueous dioxane, 0.045 M NaOH for 19.5 h (39 half-lives) and the products were isolated as described for the saturated tropane. Gc of an aliquot (A-3, 80°, 10 psi)[29] showed 3 peaks: Component 1 (r.t. 4.5 min, 30%), Component 2 (r.t. 25.4 min, 49%), and Component 3 (r.t. 39.8 min, 21%). The extracts were dried and concentrated to an oil (15 mg, 83%). The nmr ($CDCl_3$) of this oil showed resonances from at least two rearranged tosylates: 7.78 (overlapping AB doublets, J = 8 Hz), 7.32 (ABd, J = 8 Hz), 4.62 (sharp m, tosylate α-H), and 2.44 and 2.42 (s and s, NCH_3 and $PhCH_3$ of rearranged tosylates). Apparently the two α-hydrogens of the tosylates have the same chemical shift, and visual estimation of the aromatic peak areas gave *ca.* a 3:2 ratio for the two tosylates. The kinetic experiments gave a 17% yield of the rearranged tosylates at 25°. Distillation at 25° (0.05 mm) gave Component 1 contaminated by Component 2. Components 2 and 3 were molecularly distilled at 80° (0.05 mm) onto a coldfinger. Preparative gc (P-3, 100°, 9 psi) of the distilled products gave Component 1 (r.t. 3 min), which was collected with ether solvent, Component 2 (r.t. 14 min), and Component 3 (r.t. 28 min). The latter two components were collected as white solids. Three larger scale solvolyses were performed to obtain more of the three components. Component 1 was stable to distillation at *ca.* 160° (760 mm). The ir (CCl_4) showed cyclopropyl H at 3050. The nmr (CCl_4) showed 3.18 (m, $W_{1/2}$ = 7.5 Hz, 2, bridgeheads) 2.7 - 2.0 (complex m, *ca.* 4.5), 1.98 (s, 3, NCH_3), 1.5 (sharp m, *ca.* 3.5, cyclopropyl H). Component 1 contains a 3-membered ring and the nmr shows that it is symmetrical because the 2 bridgehead protons are equivalent. The most likely structure is (**35**) 9-methyl-azatetracyclo[3.3.1.$0^{2,4}$.$0^{3,7}$] nonane (9-methyl-9-azatriaxane). The nmr ($CDCl_3$) of the dihydro-analog lacking the cyclopropyl ring, 9-methyl-9-azanoradamantane, kindly provided by Sasaki, *et al.*,[32] shows 3.13 (s, 2, bridgeheads at C-1 and C-5), 2.41 (s, 3, NCH_3) 2.28 (s, 2, bridgeheads at C-3 and C-7), 1.88 and *ca.* 1.46 (unsymmetrical, broad AB q, $J_{AB}/\Delta\delta$ = *ca.* 0.45, 8, CH_2 groups). No C and H was obtained.

Component 2 was a volatile amino alcohol that was recrystallized from pentane at -78° to give a white waxy solid [mp 112 - 116° (sealed tube)] ir 3490 (m, OH, intrabonded?). Nmr showed 3.48 (m, $W_{1/2}$ = 6 Hz, 1, α-H), 3.33 (pseudotriplet, apparent J = 4.5 Hz, 1, bridgehead), 2.89 (broad s, 1, OH, exchanges with D_2O), 2.66 (m, $W_{1/2}$ = 7 Hz, 1, bridgehead), 2.52 (s, on m, 4, NCH_3 and bridgehead), 2.3 - 1.8 (2.20 and 1.95, apparent d of d, J = *ca.* 13 Hz) and 2.05 (m, 1), 1.55 (sharp m, $W_{1/2}$ = 7 Hz, 2), 1.02 (d of q, J = 13 and *ca.* 2 Hz, 1), 0.08 (d of m, J = *ca.* 13 Hz, 1). The mass sprectrum (70 eV) showed a very large water peak and 153 (54, M), 1361 (28, M-17), 110 (66, M-43), 96 (41), 94 (100, $C_6H_8N^+$), 70 (74), 58 (35), 57 (59), 42 (79, $CH_3N^+ \equiv CH$), 41 (48). Component 2 was tentatively assigned the carbinolamine structure 4-methyl-4-aza-*exo*-5-brendanol (**36**).

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14.

Component 3, was separated from Component 2 by recrystallization from ether-pentane (mp 120 - 120.5°). The ir showed 3620 (m, free OH). The nmr showed 3.92 (sharp m, $W_{1/2}$ = 3.5 Hz, 1, α–H), 3.30 (pseudotriplet, apparent J = 4 Hz, 1, bridgehead to N), 2.93 (m, $W_{1/2}$ = 9 Hz, 1, bridgehead to N), 2.80 (broad s, 1, OH, exchanges with D_2O), 2.48 (pseudotriplet, apparent J = 6 Hz, 1, bridgehead), 2.26 (s, 3, NCH_3), 2.2 - 1.7 (complex, 5), 1.55 (d, J = 12 Hz, 1), 1.33 (d of d, J = 13 and *ca.* 2 Hz, 1). The mass spectrum (70 eV) showed 153 (20, M), 136 (9, M-17), 96 (28), 95 (34), 94 (100, $C_6H_8N^+$), 83 (18), 70 (10), 57 (9), 42 (36, $CH_3N^+ \equiv CH$), 41 (13). Component 3 was tentatively assigned as 2-methyl-2-aza-*equat.*-8-noradamantanol (**37**).

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found C, 70.66; H, 9.91; N, 9.12.

Solvolysis Kinetics. Procedure A. Rates of solvolysis were followed spectrophotometrically by monitoring the disappearance of alkyl tosylate at 262 nm where the sodium tosylate and ammonium tosylate salts have a molar absorptivity 0.449 times that of alkyl tosylates in 70% aqueous dioxane.[33] The spectrophotometer was equipped with a thermostatted cell compartment (± 0.05°C) fed by two Haake Model FS Circulators. Buffered 70% aqueous dioxane solutions in 1-cm quartz cuvettes were equilibrated for 30 - 60 min. Tosylate ester (2.5 - 3 mg) was introduced in a hollow stopper and the cell was shaken for 15 sec. Absorbance was followed for at least 3 half-lives and infinity readings $(A_\infty)_{obs}$ were taken after 10 half-lives. Thirty to forty points were taken. For cases involving internal return the extent of isomerization was determined from the absorbances at zero and at infinite time. Conveniently all cases of significant isomerization produced *unreactive* tosylates. Therefore, the starting tosylates *disappear* by *two* parallel reactions: solvolysis (k_{solv}) and isomerization (k_{isomer}). The observed rate constant $k_{obs} = k_{solv} + k_{isomer}$. This is an example of Macomber's general treatment with $k_3 = 0$,[34] i.e., the isomeric tosylate does not solvolyze.

Procedure B. Solvolysis rates at elevated temperature were determined in quartz cells fitted with a graded seal to pyrex. Tosylates (0.003 M) in buffered 70% aqueous dioxane were introduced into the cells, purged with argon and sealed. A reference solution was sealed in another quartz tube. The tubes were heated in an oil bath maintained at the desired temperature ± 0.05°. Periodically the cells were withdrawn, cooled in a water bath, washed with acetone, and dried. Absorbance readings were recorded and the tubes were returned to the oil bath. "Warm-up" and "cool-down" time were assumed to be equal. About 20 points were taken for each run. Rate data were analyzed with an iterative least squares computer program[23] that produces the best first-order rate constant (k_{obs}) from the values of absorbance (A_t) and time (t) and initial estimates of k_{obs}, A_∞ and A_o. The cases studied at elevated temperature were 2-noradamantyl tosylate and 3α-hydroxymethyltropane tosylate, neither of which involve any kinetically significant isomerization, so $k_{obs} = k_{solv}$.[34]

Buffered 70% Aqueous Dioxane. The 70% by volume aqueous dioxane was prepared gravimetrically. Dioxane was purified by Fieser's procedure.[35] Distilled water was passed though a Barnstead mixed bed ion-exchange column and was degassed by argon purge at 95°. The observed weights were corrected for the bouyancy of air by use of a standard equation[36] and density data.[36b]

Solvolysis of 2-Adamantyl Tosylate. Samples (2.5-3 mg) of analytically pure 2-noradamantyl tosylate (mp 49-49.5°) were solvolyzed (*ca.* 0.003 M) in 70% aqueous dioxane containing 0.009 M diisopropylethylamine at 65° and 75° by Procedure B. Sodium hydroxide was not used as the buffer because it induces a polymer from aqueous dioxane at 60-100°. Pure samples (*ca.* 2.8 mg) of 3a-hydroxymethyltropane tosylate hydrochloride were dissolved in 70% aqueous dioxane containing 0.009 M NaOH or diisopropylethylamine to liberate the free amino tosylate (0.003 M). Solvolyses were conducted at 90° and 100° by Procedure B. The buffered reference solvents were also heated. Although all runs at 65° and above were complicated by the appearance of a broad peak at 310 nm with diisopropylethylamine buffer or at 288 with NaOH buffer, this peak was not observed in spectra of buffered reference solvents that were heated in the same manner as the solvolysis solution.

Solvolysis of 3α-Hydroxymethyltrop-6-ene Tosylate in 70% Aqueous Dioxane—0.006 M NaOH or Diisopropylethylamine. This substance was solvolyzed by Procedure A at 25° and 35°. Samples (2.7 mg) of the pure amino tosylate hydrochloride were dissolved in 70% aqueous dioxane containing 0.009 M NaOH or diisopropylethylamine to give a 0.003 M solution of the free base. The infinity absorbances readings were higher than calculated because two inert, rearranged tosylates were formed by internal return. The rearranged tosylates were inert at 25°. The solvolysis and isomerization rate constants (k_{solv} and k_{isomer}) were calculated from the fraction of internal return.

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29. The analytical (A) and preparative (P) columns used are coded as follows: A-1, 10% carbowax 20 M on Anakrom ABS; A-2, 20% MBMA [*m*-Bis-(*m*-phenoxy phenoxy) benzene and Apiezon L Grease] on Chomosorb W; A-3, 5% OV-17 on Anakrom Q; A-5, 5% G.E. XE 60 and 2% Carbowax 20 M on Anakrom AS; A-7, 20% Reoplex 400 on Chomosorb W; A-8, 20% UCON LB 1715 nonpolar on Chomosorb W; A-9, 15% Apiezon L on Chomosorb W; P-1, 5% OV-17 on Anakrom Q; P-2, 5% G.E. XE 60 and 2% Carbowax 20 M on Anakrom AS. Gc conditions are reported as (column code, column temperature, carrier gas inlet pressure). Retention times (r.t. minutes) provide information about relative ease of elution.

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